REMARKS

Claims 1-4, 6, 8-19, and 12-30 are pending in this application and have been examined. Claims 1-4, 6, 8-17, 19, 21, and 23-30 stand rejected; Claims 18 and 22 are allowed. The applicants thank the Examiner for allowing Claims 18 and 22. Claims 1, 3, 26, 27, and 29 have been canceled without prejudice to the applicants' right to prosecute the canceled claims in a subsequent patent application. Claims 2, 4, 6, 9, 11, 13, 15, 19, 23, and 25 have been amended. No new matter has been added by these amendments. Reconsideration and allowance of Claims in view of the above amendments and the following remarks is respectfully requested.

Objection to the Specification

The Examiner has noted that page 18 of the Specification is missing. Page 18 was inadvertently omitted from the PCT application. However, page 18 is present in Great Britain Application No. GB9819769.2, filed September 10, 1998, for which a claim of priority has been made. A certified copy of Great Britain Application No. GB9819769.2 was filed on May 7, 2001, with the Response to Notification of Missing Requirements. The Specification has been amended to include page 18, as shown in the British priority document. No new matter has been introduced. Applicants respectfully request withdrawal of this ground of objection.

Rejection Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected Claims 1-4, 6, 8-17, 21, 23, and 25-30 under 35 U.S.C. § 112 as lacking an enabling description in the Specification. Specifically, the Examiner states that the Specification enables methods and kits for diagnosing susceptibility to bone fracture comprising detecting the presence of the G to T polymorphism at the *Sp*1 site of the collagen Iα1 gene, but does not provide enablement for methods and kits for determining the susceptibility to bone fracture comprising detecting any allele of the collagen Iα1 gene in conjunction with detecting the baT haplotype of the vitamin D receptor gene. Similarly, the Examiner states that the

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Specification enables methods for determining susceptibility to bone fracture wherein the presence of the baT haplotype is detected, but does not provide enablement for methods for determining susceptibility to bone fracture wherein the presence of at least one of the b, a, and T alleles is indicative of an increased susceptibility to bone fracture.

Claims 1, 3, 26, 27, and 29 have been canceled. Claims 2, 4, 6, 9, 11, and 15 have been amended to correct errors in dependencies resulting from the cancellation of these claims. Claims 2, 6, and 13 have been amended to recite that the presence of the baT haplotype of the vitamin D receptor gene is detected. Claims 4, 6, 19, 23, and 25 have been amended to recite that the presence of the G to T polymorphism at the *Sp*1 site of the collagen Iα1 gene is detected. Claims 8-12, 14-17, 21, 28, and 30 depend from amended Claims 2, 4, 6, and/or 19. The Examiner has acknowledged that these limitations are supported by an enabling description in the Specification. Applicants, therefore, respectfully submit that this ground of rejection is now moot.

Rejection of Claims Under 35 U.S.C. § 103(a)

Claims 24-26 has been rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,593,833 (Morrison et al.) in view of Ahern et al., *The Scientist,* Sept. 1995, pages 1-5, or in view of Ahern et al. and Ralston (1997) *Q. J. Med.* 90:247-251.

According to the Examiner, Morrison et al. teach a method for determining the susceptibility to osteoporosis comprising the use of one or more nucleic acid molecules for amplifying a portion of the vitamin E receptor gene, means for determining whether the baT allele is present, and a means for indicating a correlation between the allele and risk of osteoporosis. Also according to the Examiner, Ralston teaches that the G to T polymorphism is associated with risk of osteoporosis, and Ahern et al. teaches pre-existing reagents are more easily used when combined in a kit. Based on this, the Examiner concludes that it would have

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been obvious to combine the primers and methods of Morrison et al. in view of Ahern et al. to generate a kit for detecting the baT haplotype of the vitamin D receptor gene. The Examiner also concludes that it would have been obvious to combine the primers and methods of Morrison et al. in view of Ralston and in further view of Ahern et al. to generate a kit for detecting the baT haplotype of the vitamin D gene and the *Sp*1 polymorphism of the collagen Iα1 gene.

Claim 26 has been canceled. Applicants respectfully submit that the burden of establishing a prima facie case of obviousness has not been met, for the following reasons. To establish a prima facie case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine the referenced teachings. In addition, there must be a reasonable expectation of success. Finally, the prior art references must teach or suggest all the claim limitations. M.P.E.P. § 706.02(j).

First, Morrison et al. discloses a correlation between bone mineral density and vitamin D receptor alleles and bone mineral density, not susceptibility to bone fracture. Although lower bone mineral density increases the risk of fractures, this does not mean that all fractures are due to low bone mineral density. In fact, the present invention has shown that the vitamin D receptor and collagen Iα1 risk alleles confer susceptibility to bone damage that is independent of bone mineral density (*see* Specification, page 4, lines 20-22; page 5, lines 22-23; page 13, lines 7-9; page 16, lines 5-8). Therefore, by disclosing a correlation between vitamin D receptor alleles and bone mineral density, Morrison et al. teaches away from the claimed invention.

Second, Morrison et al. find that the BA and/or At haplotypes are associated with low bone mineral density (Morrison et al., Column 20, lines 59-61; Column 22, lines 28-32). In contrast, applicants have found that another haplotype, the baT haplotype, is associated with an increased risk of fracture (Specification, page 4, lines 13-15). Therefore, Morrison et al. does not

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teach or suggest all the claim limitations because it does not teach or suggest a means for indicating a correlation between the baT allele and risk of osteoporosis. On the contrary, by identifying BAt as an allele associated with low bone mineral density, Morrison et al. teaches away from a correlation between the baT allele and risk or osteoporosis.

Third, the original scientific twin study on which the application for the Morrison et al. patent was based and which was published in Morrison et al. (1994) *Nature* 367:284-287, was based on erroneous genotyping (Morrison et al. (1997) (Correction) *Nature* 387:106, appended hereto as Attachment A). On re-examination, the predictive power of vitamin D receptor alleles on bone mineral density was not supported.

Because Morrison et al. does not teach or suggest all the claim limitations and, in fact, teaches away from the claimed invention, applicants submit that it would not have been obvious to combine the teachings of Morrison et al. with the kits of Ahern et al. to arrive at the invention of Claim 24, or combine the teachings of Morrison et al. and Ralston with the kits of Ahern et al. to arrive at the invention of Claim 25. Accordingly, applicants respectfully request withdrawal of this ground of rejection.

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Conclusion

In view of the above amendments and the foregoing remarks, applicants respectfully submit that all the pending claims are in condition for allowance. If any issues remain that may be expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone applicant's attorney.

Respectfully submitted,

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Enclosure:
Attachment A

I hereby certify that this correspondence is being deposited with the U.S. Postal Service in a sealed envelope as first class mail with postage thereon fully prepaid and addressed to the U.S. Patent and Trademark Office, P.O. Box 2327, Arlington, VA 22202, on the below date.

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VERSION WITH MARKINGS TO SHOW CHANGES MADE MARCH 13, 2003

In the Claims:

2. (Twice Amended) A method of determining susceptibility to bone fracture in a subject [according to claim 1] said method comprising analyzing genetic material of a subject to determine the presence of the baT haplotype of the vitamin D receptor gene, wherein the presence of the baT haplotype is indicative of an increased susceptibility to bone fracture.

4. (Twice Amended) A method of determining susceptibility to bone fracture according to claim 2[3] said method further comprising determining the presence of a G to T polymorphism at the *Sp*1 site of the collagen Iα1 gene, wherein detection of said polymorphism is indicative of an increased susceptibility to bone fracture.

6. (Three Times Amended) A method of determining susceptibility to bone fracture according to claim 2[3] said method further comprising determining the copy number of the [B/b, A/a or T/t] b, a or T alleles of the vitamin D receptor gene and/or the [S/]s allele of the collagen Iα1 gene.

9. (Twice Amended) A method according to claim 4[3], further comprising determining calcium levels in a subject.

11. (Twice Amended) A method according to claim 2[1], wherein said method is performed *in vitro*.

13. (Three Times Amended) A method of treating a subject to reduce the risk of bone fracture comprising analysing genetic material of a subject to determine [which of the B/b, A/a and T/t alleles of the *BsmI*, *ApaI* and *TaqI* sites] the presence of the baT haplotype of the vitamin D receptor gene [are present], wherein the presence of [a] the baT haplotype [comprising at least one of the b, a and T alleles] is indicative of an increased susceptibility to bone fracture, and

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treating the subject to reduce the risk of bone fracture if the subject has [a] the baT haplotype[comprising at least one of the b, a and T alleles].

15. (Twice Amended) A method according to claim 2[1], wherein the subject is a mammal.

19. (Twice Amended) A method according to claim 18, further comprising determining [which allele(s)] the presence of a G to T polymorphism at the Sp1 site of the collagen Iα1 gene[is/are present].

23. (Twice Amended) The method according to claim 22 further comprising the step of determining [which] whether the s allele of a collagen Iα1 gene is present in the subject, said kit further comprising (i) one or more nucleic acid primer molecules for amplification of a portion of the collagen Iα1 gene and (ii) means for determining [which] whether the s allele of the collagen Iα1 gene is present.

25. (Twice Amended) A kit according to claim 24, said kit further comprising (i) one or more nucleic acid primer molecules for amplification of a portion of the collagen Iα1 gene and (ii) means for determining [which] whether the s allele of the collagen Iα1 gene is present.

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Prediction of bone density from vitamin D receptor alleles

Nigel A. Morrison, Jian Cheng Qi, Akifumi Tokita, Paul J. Kelly, Linda Crofts, Tuan V. Nguyen, Philip N. Sambrook & John A. Eisman

Nature **367**, 284–287 (1994)

In order to expand our original observations of a relationship between bone density and vitamin D receptor (VDR) genotype and to examine other genes potentially involved in bone biology, we set out to recruit a larger set of identical and non-identical twins. On re-analysis of these newly collected and re-genotyped samples, we found reduced correlation of the VDR genotype with bone density in this larger sample of twin pairs. We made a formal announcement of this finding at the World Congress on Osteoporosis in Amsterdam on 20 May 1996.

As this larger twin sample included some of the twins reported earlier, we re-examined the original samples and found that in a proportion of these twins the genotype (by PCR) on new leukocyte DNA samples differed from those obtained on the earlier leukocyte DNA samples (also by PCR). It seems most likely that the mis-classifications arose from mis-genotyping of DNA samples between extraction and PCR analysis. We emphasize that the other major part of the paper, showing a genotype effect in a population sample, is not affected by such mis-genotyping.

A role of the VDR alleles in bone biology has been reproduced in a wide range of clinical and physiological studies. Other studies have found an effect but in the reverse direction and some have found no effect on bone density or turnover or on osteoporosis prevalence. Thus, while there is disagreement about the strength of the effect, these and other studies in several population samples support the role of the VDR in the polygenic inheritance of bone density. □

Diverse sources of hippocampal unitary inhibitory postsynaptic potentials and the number of synaptic release sites

Eberhard H. Buhl, Katalin Halasy & Peter Somogyi

Nature **368**, 823–828 (1994)

The scale bar for all panels of Fig. 4 of this Article was 0.4 μm, and not 0.2 μm as published. □

Attachment A